11. (Amended) A recombinant DNA sequence encoding a human thyroid peroxidase which is secreted from a cell.

REMARKS

Claims 11 to 15 are pending but rejected. Claim 37 has been withdrawn from consideration.

A. Objections to Oath/Declaration, Specification, and Lack of Certified Copy of Priority Documents

The undersigned has assumed the prosecution the above patent application from the prior attorney, Henry N. Wixon. The undersigned just noticed that the Declaration by the Inventors, which the July 21, 1998 "Response under 37 CFR §§ 1.111 and 1.115" indicated to have been filed, is missing from the file transferred to the undersigned. The undersigned has requested attorney Wixon for clarification of the priority claims. As soon as the information has been obtained, the undersigned will submit another Declaration, the necessary amendment to the specification, and certified copies of priority documents. Meanwhile, it is respectfully requested thanks the Examiner hold the objections in abeyance. The undersigned understands that the Examiner is holding the objections to the specification, in abeyance, pending notification of allowable subject matter.

B. Claim Rejections under 35 U.S.C. §112, First Paragraph

Claims 11 - 14 remains rejected under 35 U.S.C. §112, first paragraph. With regard to this rejection, applicant maintains his position in the previous July 21, 1998 "Response under 37 C.F.R. §§ 1.111 and 1.115". The Examiner feels that the application only discloses one example of a mutated human thyroid peroxidase (hTPO) and is thus insufficient to enable the broad claims. "[t]here are no parameters described and no teaching of how to determine which sites are appropriate for mutation so that DNA sequences could be made and selected for testing and evaluation to determine if the mutated, expressed protein will be soluble and function as claimed." (Emphasis ours,

Office Action, p. 5, lines 2 - 7).

However, the Examiner also states that: "the specification clearly teaches site directed mutagenesis of a stop codon immediately upstream of the putative transmembrane domain to convert hTPO from membrane bound to a soluble version that is immunologically and enzymatically active and immunologically intact (see p. 8, lines 27 - page 9 line 6) and teaches assays to demonstrate the immunological and enzymatic activity of the soluble hTPO (see pages 58-60)...". Thus, claims 12 to 13 should be allowable because they specifically claim a recombinant hTPO DNA sequence which "possesses a stop codon upstream from a transmembrane domain" (claim 12) and even more specifically one which "possesses a stop codon upstream from nucleotides encoding amino acid residues 846-870 as shown in figure 7." (claim 13).

Further, once the specification has clearly taught and demonstrated that site directed mutagenesis could produce a soluble version of hTPO, one skilled in the art can employ, e.g., the site directed mutagenesis shown in the specification to systematically mutate different sites of the disclosed recombinant hTPO DNA sequence (particularly in the short and limited regions claimed by claims 12 and 13). The resultant mutated sequences can then be systematically and routinely assayed for activities using the clearly set out assays of the specification.

Undue experimentation is absent when the experimentation is routine and accepted in the art, it is not predicated upon the number of repetitious routine experiments that must be undertaken. The court has found no undue experimentation in massive production and screening of hybridomas to obtain antibodies possessing the claimed characteristics. In re Wands, 8 USPQ 2d, 1400 (1988), finds that immunizing mice and producing hybridoma and screening for antibody of a particular specificity is not undue experimentation because it is routine and accepted in the art.

General methods of constructing vectors and transfecting different host cells are well known in the art (as the cited references show). Applicant does not need to set out methods, vectors, hosts that are known in the art, nor methods, vectors, hosts that are known not to work in the art. The expertise of one skilled in the art in the recombinant DNA area is very high. "It is impractical and unreasonable to require a patentee to set out an extended list of precise combinations and formulae since one skilled in the art would avoid obvious inoperative combinations. Ex parte Cole, 223 U.S.P.Q. 94, 95-96 (TTAB 1983); Lever Bros. Co. V. Procter & Gamble Mfg. Co., 60 USPQ 76, 80-81 (4th Cir.

1943); In re Kroekel, 183 USPQ 610, 612 (C.C.P.A. 1974). '[I]t is not a function of the claims to specifically exclude ... possible inoperative substances.' Atlas Power Co. 224 USPQ at 414." Syntex Inc. v. Paragon Optical Inc.,7 USPQ 2d 1001,1035 (Dist Ct., Az 1987)[Federal citations omitted]. See also, Ex Parte Mark, 12 USPQ 2d 1905, at 1906-7 (US Pat and Trademark Office, Board of Patent Appeals and Interferences, 1989): "The record before us establishes that for a given protein having cysteine residues, one skilled in the art would be able to routinely determine whether deletion or replacement of the cysteine residues would result in a mutein which is within the claim on appeal....The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity."

For the present claims, if one skilled in the art desires to use a certain vector or host cell other than that specifically taught in the specification, once he has determined the correct mutated nucleotides based on the methods shown in the specification (e.g., by using site mutagenesis, CHO cells, and the disclosed assay), he can then incorporates the nucleotides into his desired vector and transfects his desired host cell using methods known in the art, and then employs the disclosed routine assay to determine if the transfected cell secretes the TPO. He may also add a signal sequence, if he wishes, and uses the routine assay to determine whether the desired hTPO is obtained. As the Examiner indicates, the hindsight gained from the applicant's teaching in combination with the prior art teaches "the means ... to successfully produce a recombinant DNA encoding a secretable thyroid peroxidase...." (Office Action, p. 6, lines 18-21; see Office Action, p. 6, lines 8 - 9, for the Examiner's use of hindsight based on the applicant's invention).

The Examiner cites Brenner v. Manson, 148 USPQ 689 (Supreme Court, 1966) for stating "a patent is not a hunting license". Brenner v. Manson addresses 35 USC 102 (the utility requirement), not 35 USC 112, first paragraph at issue here. The court's comment of "a patent is not a hunting license" refers to its determination that a patent should not issue: "Until the process claim has been reduced to production of a product shown to be useful..." Id., at 695, right col (Emphasis ours). Brenner v. Manson actually supports the present claims because the present invention has actually produced a useful product, as recognized by the Examiner (Office Action, p. 5, lines 5 - 6).

In view of the above, the applicant respectfully submits that the claims are enabled and requests that the Examiner withdraw the rejection.

C. Rejections under 35 U.S.C. §112, Second Paragraph

Complying with item 11 of the Office Action, applicant hereby amends claim 11 to recite "A recombinant DNA sequence encoding a human thyroid peroxidase..." which the Examiner indicates would obviate the indefiniteness rejection.

With regard to items (a) and (c), applicant maintains his position in the previous July 21, 1998 "Response under 37 C.F.R. §§ 1.111 and 1.115". To reiterate, one skilled in the art would understand what "human thyroid peroxidase" and "a stop codon upstream" mean in light of the specification. See, In re Marosi, Stabenow, and Schwarzmann, 218 USPQ 289, 292(Fed Cir, 1983): "It is well established that 'claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their 'broadest *reasonable* interpretation.'" See also, Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 867 (Fed. Cir. 1985): "[c]laims should be construed as they would be by those skilled in the art." One skilled in the art would use such "reasonable interpretation", which includes common sense, in construing the claims, such as in determining whether a nucleotide sequence with a stop codon five amino acids after the start codon would produce a protein that could still be reasonably considered a hTPO within the scope of the patent application.

D. Rejection under 35 U.S.C. §103

Claims 11 - 15 are rejected under 35 U.S.C. §103 as being unpatentable over the cited references. The applicant respectfully traverses the rejection and maintain his position as disclosed in his previous July 21, 1998 "Response under 37 C.F.R. §§ 1.111 and 1.115".

Further, applicant traverses the rejections because the Examiner wrongfully applies the obviousness rejection based on hindsight. The Examiner mistakenly believes that these rejections are appropriate because "some degree of hindsight is permissible in making rejections under 35 USC 103,..." (Office Action, p. 6, lines 8 -9). Applicant is unaware of any legal authority supporting the Examiner's position. On the contrary, the legal

authorities that applicant are aware of state exactly the opposite, see e.g., Medtronic, Inc. v Daig. Corp., 227 USPQ 509, 535 (D.Minn. 1985), affirmed, 229 USPQ 664 (Fed. Cir. 1986): "Hindsight . . . is quite improper when it involves a question of obviousness. To use the patent in suit as a guide through all the morass of prior art references, combining the right references in the right way to arrive at the result of the claim in suit is . . . also quite improper."; see also In re Fine, 5 USPQ 2d 596 (Fed. Cir. 1988): "One cannot use hindsight construction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." Applicant respectfully requests that the Examiner either provides the legal authority in support of her position or withdraw the rejection because her rejection is impermissibly tainted by her use of hindsight.

Absent hindsight, the references, alone or in combination does not teach nor suggest the present invention. As the Examiner has explained in her January 21, 1998 Office Action (Paper No. 12) in the parent application: "Since it is well known that the signals for nucleic acid translation and transcription, codon usage, and protein processing and targeting are not universally recognized by all classes or organisms, it could not be predicted that any thyroid peroxidase sequence would be produced and secreted by any host cell which it was transformed..." (Emphasis ours, Paper No. 12, p. 6 - p. 7). Thus, until applicant has demonstrated the success his invention and therefore the expectation that it would work in the other host cells, the prior art has not provided any expectation that applicant's claimed invention would succeed. As In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988) states: "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." (Emphasis ours). The claims cannot be rejected if the references do not show that there was a reasonable expectation of success, see In re O'Farrell, 853 F. 2d 894, 903-04, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). Mere motivation is insufficient to support an obviousness rejection.

To expand on the Examiner's observation, the behavior of one protein or nucleic acid does not predict the behavior of another protein or nucleic acid, especially if they are from different organisms, serve different functions, are of different complexities and properties, have different structures and foldings etc., not to mention different processing etc., behaviors. Thus, the following references are irrelevant to the present invention because they pertain to nucleic acids and organisms, vectors and host cells that are unrelated to that of the present invention and therefore cannot be used to predict whether the

truncated hTPO could be secreted: (1) Lee et al uses fusions between a virus' long terminal repeat and a mouse dihydrofolate reductase cDNA construct; (2) Ellis et al uses insulin receptor tyrosine residues. Further, neither Lee et al nor Ellis et al addresses the secretion of a truncated protein with a stop codon upstream; (3) Rose et al discloses the secretion viral G protein without its carboxyl terminus, not mammalian nor human TPO. Rose observes that "... The time required for secretion of the truncated protein seems unusually long.... it seems possible that a specific domain of G protein required for rapid transport to the cell surface has been lost in this deleted molecule, or that the deleted protein may fold into an unusual conformation that impedes transport." (Rose et al., p. 780, left col.). Thus, Rose et al shows that it is not at all obvious that applicant could have obtained the secretion of a truncated hTPO, given that the truncation might have removed the section responsible for transport of the protein or cause unusual conformation that impedes its transport; (4) Similarly, EP 0139417 (hereinafter referred to as "EP") deals with the truncated virus, not mammalian nor human TPO. EP cites only Rose et al for an example of secreted truncated protein and EP notes that Rose et al's protein is "slowly secreted" (EP, p. 2, lines 7-10). Significantly, even though Rose et al shows a secretable truncated viral protein, EP still considers its truncated secreted viral protein to be nonobvious. Applicant's invention is even further removed from these two references because it deals with a human TPO.

The three references relating to TPO are Seto et al., Liebert et al, and Magnusson et al. None of the three references, alone or in combination, teaches or suggests a recombinant DNA sequence which encodes hTPO which is secreted from a cell (claim 11), or one with a stop codon upstream from a transmembrane domain (claim 12), or the stop codon is specifically "upstream from nucleotides encoding amino acid residues 846-870 as shown in figure 7" (claim 13). Further, Magnusson et al discloses a porcine thyroid peroxidase with a carboxyl-terminal transmembrane domain (a protein and organism different from that of the present invention). Until the present invention, "There has heretofore been no functional proof that the hTPO hydrophobic region 846-870 corresponds to a transmembrane domain. The present invention demonstrates the existence of a transmembrane domain in hTPO..." (Specification, p. 8, lines 28-31).

Even if, arguendo, all the references are combined as suggested by the Examiner,

the combination at most suggests that the location of the transmembrane domain of the hTPO may possibly be (but not with a reasonable expectation of certainty) the same as in the porcine TPO, and if this region is truncated, the resultant nucleotide may encode a secretable hTPO, but then it may not, because the region responsible for transportation of the hTPO may be so disrupted or the folding of the resultant protein may be so "unusual" (see Rose et al, above) that its secretion would be slowed to nonexistent (see Rose et al's observation and EP's comment on Rose et al, discussed above) or there may be no secretion due to the numerous factors that could go wrong with the particular vector or host cell chosen (as theorized by the Examiner). These numerous factors include signals for nucleic acid translation and transcription, codon usage, and protein processing and targeting that are not universally recognized by all classes or organisms, such that it could not be predicted that any thyroid peroxidase sequence would be produced and secreted by any host cell which it was transformed (Paper No. 12, p. 6 - p. 7). Thus, the teachings of the cited references (e.g., Rose et al, and EP) with regard to the other hosts, vectors, and proteins cannot be predicted to similarly apply to hTPO.

Thus, at most, the references only show that it is "obvious to try" the present invention. However, "obvious to try" is not the proper legal standard for finding of obviousness. Even if "obvious to try" is found, the claims cannot be rejected if the references do not show that there was a reasonable expectation of success. See, In re O'Farrell, 853 F. 2d 894, 903-04, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). Such is the case here.

CONCLUSION

In view of the above discussion, applicants respectfully submit that the claimed invention is enabled, definite, and nonobvious and that the amendment has overcome the Examiner's objections/rejections.

Respectfully submitted,

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